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Beyond Low-Density Lipoprotein Cholesterol

Respective Contributions of Non–High-Density Lipoprotein Cholesterol Levels, Triglycerides, and the Total Cholesterol/High-Density Lipoprotein Cholesterol Ratio to Coronary Heart Disease Risk in Apparently Healthy Men and Women

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Objectives This study was designed to test the hypothesis that at any low-density lipoprotein cholesterol (LDL-C) level, other lipid parameters such as non–high-density lipoprotein cholesterol (HDL-C) levels, triglyceride (TG) levels, and the total cholesterol (TC)/HDL-C are still associated with an increased coronary heart disease (CHD) risk.

Background Although LDL-C is considered to be the primary target of lipid-lowering therapy, other parameters of the lipoprotein-lipid profile may more closely associated with CHD risk.

Methods In the EPIC (European Prospective Investigation Into Cancer and Nutrition)-Norfolk prospective population study, 21,448 participants without diabetes or CHD between age 45 and 79 years were followed for 11.0 years. A total of 2,086 participants developed CHD during follow-up.

Results Among individuals with low LDL-C levels (<100 mg/dl), after adjustment for age, sex, smoking, systolic blood pressure, waist circumference, physical activity, and hormone replacement therapy (in women), those with non–HDL-C >130 mg/dl had a hazard ratio (HR) for future CHD of 1.84 (95% confidence interval [CI]: 1.12 to 3.04) when compared with those with non–HDL-C levels <130 mg/dl. In a similar model, individuals with TG levels >150 mg/dl had an HR of 1.63 (95% CI: 1.02 to 2.59) when compared with those with TG levels <150 mg/dl, and individuals with a TC/HDL-C ratio >5 had an HR of 2.19 (95% CI: 1.22 to 3.93) when compared with those with a TC/HDL-C ratio <5.

Conclusions In this prospective study, independently of their plasma LDL-C levels, participants with high non–HDL-C levels, high TG levels, or with an elevated TC/HDL-C ratio were at increased CHD risk. CHD risk assessment algorithms as well as lipid targets of lipid-lowering trials may also need to consider other easily available parameters such as non–HDL-C. (J Am Coll Cardiol 2010;55:35–41) © 2010 by the American College of Cardiology Foundation

Over the past decades, numerous population-based and intervention studies have identified low-density lipoprotein cholesterol (LDL-C) as a key risk factor for coronary heart disease (CHD) (1–5). Based on this evidence, guidelines of the National Cholesterol Education Program-Adult Treatment Panel III suggest that first-line therapy should be directed toward LDL-C lowering (6,7). However, although many trials have documented the benefits of lowering plasma LDL-C levels for the primary and secondary prevention of CHD, studies have shown that individuals reaching their LDL-C target may still be at increased CHD risk if they have detrimental levels of other parameters of the lipoprotein-lipid profile (8). In this regard, it has recently been proposed that other lipid parameters such as cholesterol levels in lipoproteins other than high-density lipopro-

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Abbreviations and Acronyms

CHD = coronary heart disease
CI = confidence interval
HDL = high-density lipoprotein
HDL-C = high-density lipoprotein cholesterol
HR = hazard ratio
LDL = low-density lipoprotein
LDL-C = low-density lipoprotein cholesterol
TC = total cholesterol
TG = triglyceride

teins (HDLs) (i.e., non–high-density lipoprotein cholesterol [HDL-C] levels), triglyceride (TG) levels, or the total cholesterol (TC) to HDL-C ratio could better predict cardiovascular outcomes in patients on LDL-C–lowering therapy (8,9). However, there is a lack of epidemiological data to suggest that the aforementioned parameters of the lipoprotein-lipid profile could better predict CHD risk than LDL-C in asymptomatic individuals.

The objective of the present study was to investigate the relative contributions of several indexes of the lipid-lipoprotein profile, namely LDL-C, non–HDL-C, and TG levels as well as the TC to HDL-C ratio, to the risk of CHD in a study cohort representative of a contemporary Western population. In addition, we tested the hypothesis that independently from LDL-C levels, individuals with high non–HDL-C levels, high TG levels, or with a high TC to HDL-C ratio still have an increased risk of developing CHD.

Methods

Study design. The EPIC (European Prospective Investigation Into Cancer and Nutrition)-Norfolk study is a population-based study of 25,668 men and women between 45 and 79 years of age who are residents of Norfolk, United Kingdom, and who completed a baseline questionnaire survey and attended a clinic visit (10). Participants were recruited from age-sex registers of general practices in Norfolk as part of the 10-country collaborative EPIC study designed to investigate dietary and other determinants of cancer. Additional data were obtained in the EPIC-Norfolk study to enable the assessment of determinants of other diseases. The study cohort was closely similar to United Kingdom population samples with regard to many characteristics, including anthropometry, blood pressure, and lipids, but with a lower proportion of smokers.

The design and methods of the study have been described in detail (10). In short, eligible participants were recruited by mail. At the baseline survey conducted between 1993 and 1997, participants completed a detailed health and lifestyle questionnaire. Blood was taken by venipuncture into plain and citrate tubes. Blood samples were processed for various assays at the Department of Clinical Biochemistry, University of Cambridge, or stored at −80°C. Nonfasting serum levels of TC, HDL-C, and TG were measured on fresh samples with the RA 1000 (Bayer Diagnostics, Basingstoke, United Kingdom), and LDL-C levels were calculated with the Friedewald formula (11). Non–HDL-C was calculated by subtracting HDL-C levels from TC levels. All individuals were flagged for mortality at the U.K. Office of National Statistics, with vital status ascertained for the entire cohort. Death certificates for all decedents were coded by trained nosologists according to the International Classification of Diseases (ICD)-Ninth Revision. Death was considered due to CHD if the underlying cause was coded as ICD 410 to ICD 414. These ICD codes encompass the clinical spectrum of CHD—unstable angina, stable angina, and myocardial infarction. Previous validation studies in our cohort indicated high specificity for such case ascertainment (12). In addition, participants admitted to hospital were identified by their unique National Health Service number by data linkage with the ENCORE (East Norfolk Health Authority database) registry, which identifies all hospital contacts throughout England and Wales for Norfolk residents. Participants were identified as having CHD during follow-up if they had a hospital admission and/or died with CHD as an underlying cause. Individuals with diabetes mellitus were excluded from the present analyses. Diabetes mellitus status was ascertained by means of the following: 1) self-report of diabetes medication use; 2) diabetes medication brought to the baseline health check; 3) the participant indicating modification of the diet in the past year because of diabetes; or 4) the participant indicating adherence to a diabetic diet. The Norwich District Health Authority Ethics Committee approved the study, and all participants gave signed informed consent. We report results of 21,448 individuals without CHD at baseline who were followed up to March 2007, an average of 11.0 ± 2.0 years.

Statistical analyses. Baseline characteristics were compared between participants who developed CHD during follow-up versus those who did not using an unpaired Student *t* test. Cox regression analysis was used to calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the risk of future CHD in pre-specified categories of LDL-C (<100 mg/dl, 100 to 129.9 mg/dl, 130 to 159.9 mg/dl, and ≥160 mg/dl as suggested by the National Cholesterol Education Program-Adult Treatment Panel III [7]), non–HDL-C (<130 mg/dl, 130 to 159.9 mg/dl, 160 to 189.9 mg/dl, and ≥190 mg/dl [thresholds for non–HDL-C are parallel to those for LDL-C but the former are 30 mg/dl higher]), and TG levels (<150 mg/dl, 150 to 199.9 mg/dl, 200 to 249.9 mg/dl, and ≥250 mg/dl), and of the TC to HDL-C ratio (<4.00, 4.00 to 4.99, 5.00 to 5.99, and >6.00). Because TG levels had a skewed distribution, values were log-transformed before being used as a continuous variable in this model. Hazard ratios were also calculated per 1-SD increase of LDL-C, non–HDL-C, TG levels, and TC to HDL-C ratio. The SD units corresponded to 40.2 mg/dl for LDL-C, 45.2 mg/dl for non–HDL-C, 74.3 mg/dl for log-transformed TG and 1.56 for the TC to HDL-C ratio. Cox regression analysis was also used to calculate HR for future CHD in individuals classified on the basis of LDL-C levels (<100 mg/dl, 100 to

129.9 mg/dl, 130 to 159.9 mg/dl, and ≥160 mg/dl) with high non–HDL-C (maximal LDL-C level plus 30 mg/dl), TG (≥150 mg/dl), and TC to LDL-C ratio (≥5.00). All HRs were adjusted for age, sex (when sexes were combined), smoking, waist circumference, physical activity, systolic blood pressure (when sexes were combined), and hormone replacement therapy use (for women only). Kaplan-Meier survival curves were computed for participants classified into 4 groups—above or below the median for: 1) LDL-C and non–HDL-C levels; 2) LDL-C and TG levels; and 3) LDL-C levels and the TC to HDL-C ratio. Differences between curves were assessed by log-rank test. Statistical analyses were performed using SPSS software (version 12.0.1, SPSS Inc., Chicago, Illinois). A p value <0.05 was considered statistically significant.

Results

Among the 9,348 male study participants, 1,310 developed CHD during follow-up of 11.0 years, and among the 12,100 women, 776 developed CHD during follow-up. Baseline characteristics of participants who developed CHD versus those who did not are shown in Table 1 for men and women separately. In both sexes, participants who developed CHD were older and had higher blood pressure and a more detrimental lipid profile than those who remained free from CHD during follow-up.

Table 2 presents the adjusted HRs for future CHD according to LDL-C levels, non–HDL-C levels, TG levels, or TC to HDL-C ratio. After adjustment for age, smoking, waist circumference, physical activity, systolic blood pressure (for sexes combined), and hormone replacement therapy use (for women), individuals with elevated lipid levels were at increased risk of CHD. Non–HDL-C was the better predictor for risk of future CHD with increasing categories of respective lipoproteins (HR: 2.39, 95% CI: 1.91 to 2.99). We found no significant interaction between sex and lipid categories.

In Table 3, the HRs for future CHD associated with a 1-SD increase of the same lipid indexes are shown. Again, increasing lipid levels were associated with an increased CHD risk. When sexes were analyzed together, the risk associated with 1-SD increase of non–HDL-C (HR: 1.54 [95% CI: 1.35 to 1.74, $p < 0.001$]) was statistically higher than the risk associated with 1-SD increase of either LDL-C (HR: 1.22 [95% CI: 1.17 to 1.27, $p < 0.001$]), TG (HR: 1.14 [95% CI: 1.09 to 1.19, $p < 0.001$]), or the TC to HDL-C ratio (HR: 1.19 [95% CI: 1.14 to 1.24, $p < 0.001$]). We also tested for interaction between sex and lipids and found that there was a significant interaction between sex and LDL-C in predicting CHD risk ($p = 0.02$). There was no other sex-lipid interaction for the other lipids.

In order to investigate whether individuals with high non-HDL levels, high TG levels, or with a high TC to HDL-C ratio were at increased risk irrespective of LDL-C levels, we classified our study sample in 4 groups according

Table 1 Baseline Characteristics of Men and Women Included in EPIC-Norfolk Who Developed CHD During the Study Follow-Up Versus Participants Who Did Not Develop CHD

	Men		Women	
	Without CHD	With CHD	Without CHD	With CHD
Number of participants	8,038	1,310	11,324	776
Age, yrs	58 ± 9	64 ± 8*	58 ± 9	66 ± 7*
Smoking				
Current	11.6 (934)	15.2 (199)*	11.2 (1,267)	14.0 (109)*
Past	52.1 (4,189)	59.8 (784)*	31.4 (3,557)	35.8 (278)*
Never	36.3 (2,915)	25.0 (327)*	57.4 (6,500)	50.1 (389)*
Hormone replacement therapy	N/A	N/A	21.5 (2,439)	12.0 (93)*
Physical activity				
Active	23.9 (1,924)	17.6 (231)*	16.4 (1,853)	9.1 (71)*
Moderately active	24.0 (1,932)	21.5 (281)*	23.3 (2,644)	17.0 (132)*
Moderately inactive	25.0 (2,010)	22.5 (295)*	32.5 (3,681)	29.8 (231)*
Inactive	27.0 (2,172)	38.4 (503)*	27.8 (3,146)	44.1 (342)*
Waist circumference, cm	95 ± 9	98 ± 10*	81 ± 10	86 ± 11*
Systolic blood pressure, mm Hg	136 ± 17	143 ± 19*	133 ± 18	143 ± 19*
Diastolic blood pressure, mm Hg	84 ± 11	86 ± 12*	80 ± 11	84 ± 12*
TC, mg/dl	230.1 ± 40.9	242.1 ± 41.3*	240.5 ± 45.2	261.8 ± 47.5*
LDL-C, mg/dl	149.8 ± 37.1	161.0 ± 37.1*	153.3 ± 41.7	172.2 ± 43.6*
HDL-C, mg/dl	48.3 ± 13.1	45.6 ± 12.4*	61.0 ± 16.2	56.8 ± 15.4*
Non–HDL-C, mg/dl	181.9 ± 41.7	196.1 ± 49.0*	179.5 ± 47.1	205.0 ± 48.3*
TC/HDL-C	5.07 ± 1.54	5.61 ± 1.59*	4.22 ± 1.43	4.93 ± 1.54*
TG, mg/dl	150.4 (106.2–203.5)	159.3 (115.0–221.2)*	115.0 (88.5–168.1)	150.4 (115.0–212.4)*

Data are presented as mean ± SD, % (n), or median (interquartile range). *Significantly different from participants without coronary heart disease (CHD) ($p \leq 0.05$).

EPIC = European Prospective Investigation of Cancer; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; N/A = not applicable; TC = total cholesterol; TG = triglyceride(s).

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Table 2 HRs for Future Coronary Heart Disease According to LDL-C, Non–HDL-C, and Triglyceride Levels and the TC to HDL-C Ratio

LDL-C, mg/dl	<100	100–129.9	130–159.9	>160	p Value
Total, person-yrs	16,924	52,205	72,062	93,850	
HR	1.00	1.15 (0.90–1.46)	1.30 (1.03–1.64)	1.81 (1.45–2.27)	<0.001
Men, person-yrs	6,751	22,389	33,138	38,130	
HR	1.00	1.15 (0.86–1.55)	1.38 (1.04–1.82)	1.95 (1.49–2.56)	<0.001
Women, person-yrs	10,174	29,844	38,896	55,705	
HR	1.00	1.08 (0.71–1.65)	1.07 (0.72–1.61)	1.41 (0.95–2.09)	0.001
Non–HDL-C, mg/dl	**<130**	**130–159.9**	**160–189.9**	**>190**	
Total, person-yrs	6,374	52,394	64,262	92,023	
HR	1.00	1.43 (1.13–1.83)	1.60 (1.27–2.02)	2.39 (1.91–2.99)	<0.001
Men, person-yrs	8,501	21,736	29,782	40,375	
HR	1.00	1.59 (1.16–2.18)	1.82 (1.34–2.46)	2.65 (1.98–3.55)	<0.001
Women, person-yrs	17,859	30,654	34,451	51,650	
HR	1.00	1.15 (0.79–1.69)	1.19 (0.83–1.71)	1.81 (1.28–2.56)	<0.001
TG, mg/dl	**<150**	**150–199.9**	**200–249.9**	**>250**	
Total, person-yrs	137,039	48,985	26,660	22,375	
HR	1.00	1.25 (1.12–1.39)	1.26 (1.10–1.43)	1.57 (1.38–1.79)	<0.001
Men, person-yrs	49,243	23,952	14,093	13,097	
HR	1.00	1.17 (1.02–1.35)	1.20 (1.02–1.41)	1.49 (1.27–1.74)	<0.001
Women, person-yrs	87,786	25,016	12,562	9,277	
HR	1.00	1.31 (1.10–1.56)	1.29 (1.03–1.61)	1.61 (1.29–2.01)	<0.001
TC/HDL-C	**<4.00**	**4.00–4.99**	**5.00–5.99**	**>6.00**	
Total, person-yrs	89,089	61,443	42,140	42,354	
HR	1.00	1.36 (1.20–1.56)	1.66 (1.45–1.91)	2.14 (1.88–2.44)	<0.001
Men, person-yrs	23,007	27,914	22,833	26,632	
HR	1.00	1.32 (1.09–1.58)	1.74 (1.45–2.09)	2.15 (1.81–2.56)	<0.001
Women, person-yrs	66,041	33,546	19,311	15,722	
HR	1.00	1.40 (1.16–1.69)	1.46 (1.18–1.81)	2.02 (1.65–2.48)	<0.001

Values are n or hazard ratio (HR) (95% confidence interval). HRs were obtained after adjustments for age, sex (total), smoking, waist circumference, physical activity, systolic blood pressure (total), and hormone replacement therapy use (women).

Abbreviations as in Table 1.

to LDL-C targets suggested by the National Cholesterol Education Program-Adult Treatment Panel III. Table 4 shows that, even for participants with LDL-C <100 mg/dl, individuals with high non–HDL-C levels, high TG levels, or with a high TC to HDL-C ratio were at increased risk for CHD.

Finally, Kaplan-Meier survival curves showing the event-free survival during follow-up were calculated for study participants classified on the basis of LDL-C and TG levels (Fig. 1A), LDL-C and non–HDL-C levels (Fig. 1B), and LDL-C levels and the TC to HDL-C ratio (Fig. 1C). This figure shows that that LDL-C does not help to discriminate those who developed CHD from those who did not once non–HDL-C is taken into consideration. On the other hand, LDL-C and TG levels as well as LDL-C and the TC to HDL-C ratio appear to be independently associated with risk of future CHD.

Discussion

We observed that among apparently healthy men and women in a cohort representative of a contemporary Western population, non–HDL-C, TG, and the TC to HDL-C ratio were more strongly associated with risk of future CHD than was LDL-C. We also found that at any LDL-C level, individuals with elevated non–HDL-C levels, elevated TG levels, or with an increased TC to HDL-C ratio were still at an increased risk of developing CHD.

A number of studies have investigated the relationships between LDL-C and non–HDL-C as well as TG levels to the risk of CHD (13). In a case-control study sample of the Health Professionals Follow-up Study, the HR for future CHD (top quintile vs. bottom quintile) was 2.76 (95% CI: 1.66 to 4.58) for non–HDL-C, 2.41 (95% CI: 1.43 to 4.07) for TG, and 1.81 (95% CI: 1.12 to 2.93) for LDL-C levels, suggesting that these other traditional lipid parameters in CHD risk prediction may be more strongly associated with CHD risk than LDL-C is. Our results are also in agreement with those of the Lipid Research Clinics Program Longitudinal Follow-up Study, which investigated the relationships between several lipid parameters and the risk of cardiovascular mortality over a 19-year follow-up in 2,406 men and 2,058 women (14). Compared with men with non–HDL-C levels <160 mg/dl, men with non–HDL-C levels >220 mg/dl had an HR for future CHD of 2.14 (95%

Table 3 Hazard Ratios for Future CHD According to 1-SD Increase in LDL-C, Non–HDL-C, and TG Levels and the TC to HDL-C Ratio

	Hazard Ratio	95% CI	p Value
LDL-C			
Total	1.22	1.17–1.27	<0.001
Men	1.27	1.20–1.35	<0.001
Women	1.12	1.05–1.20	0.001
Non–HDL-C			
Total	1.54	1.35–1.74	<0.001
Men	1.46	1.25–1.71	<0.001
Women	1.59	1.27–1.98	<0.001
Triglycerides*			
Total	1.14	1.09–1.19	<0.001
Men	1.12	1.07–1.18	<0.001
Women	1.15	1.07–1.24	<0.001
TC/HDL-C			
Total	1.19	1.14–1.24	<0.001
Men	1.17	1.12–1.23	<0.001
Women	1.23	1.13–1.35	<0.001

Hazard ratios were obtained after adjustments for age, sex (total), smoking, waist circumference, physical activity, systolic blood pressure (total), and hormone replacement therapy use (women).
*On log-transformed values.
CI = confidence interval; other abbreviations as in Table 1.

CI: 2.50 to 3.04), and compared with men with LDL-C levels <130 mg/dl, men with LDL-C levels >190 mg/dl had an HR for future CHD of 1.77 (95% CI: 1.22 to 2.59). Results were similar among women. In men of the Framingham Offspring Study, 1-SD increment of LDL-C was associated with an increased CHD risk (HR: 1.11 [95% CI: 0.97 to 1.27]) and the HRs for future CHD were 1.22 (95% CI: 1.06 to 1.40) and 1.39 (95% CI: 1.22 to 1.58), respectively, for non–HDL-C levels and the TC to HDL-C ratio (15). In women, the HRs for future CHD were 1.20 (95% CI: 0.99 to 1.46), 1.28 (95% CI: 1.06 to 1.56), and 1.39 (95% CI: 1.17 to 1.66), respectively, for 1-SD increment of LDL-C, non–HDL-C, and the TC to HDL-C ratio. The importance of the TC to HDL-C ratio as opposed to other parameters of the lipoprotein-lipid profile was also highlighted in the Québec Cardiovascular Study as well as in the Women's Health Study (16). These prospective studies are consistent in showing that parameters of the lipoprotein-lipid profile may be more closely associated with CHD incidence than LDL-C. However, the current guidelines recommend LDL-C as the primary lipid target, and therefore the main question remains if there is any increased risk associated with other lipids even at low levels of LDL-C. In our study, non–HDL-C levels appeared to be the most important risk factor beyond LDL-C. We believe than an important strength of the present study resides in the fact that we have quantified the risk associated with these lipid parameters in each category of LDL-C levels, from low (<100 mg/dl) to high (>160 mg/dl). To the best of our knowledge, the present study is the first prospective, population-based study to suggest that the risk associated with elevated non–HDL-C levels, TG levels, or with an elevated TC to HDL-C ratio is present in any given LDL-C category, and especially in participants with low LDL-C levels.

Our results also provide epidemiological evidence to recent post-hoc analyses of important lipid-lowering trials that have reported that independently from LDL-C levels, individuals with either high non–HDL-C (8) or high TG levels (17) could nevertheless be at increased CHD risk. In the present analyses, we found that levels of LDL-C do not provide any additional risk for CHD to non–HDL-C whereas at any given LDL-C level, non–HDL-C levels were associated with higher risk of CHD.

Study limitations. It is important to point out that lipid levels were determined in nonfasting samples that were not obtained after a standardized meal. This may have caused random misclassification of study participants and therefore could have reduced our ability to detect associations between either TG or non–HDL-C levels and CHD risk. However, recent studies have highlighted the usefulness of nonfasting TG levels in CHD risk prediction, possibly because metabolic perturbations may be most pronounced in the post-prandial state (18,19). Moreover, in daily life, individuals are at the post-prandial state for the majority of the time. However, despite being nonfasting, TG levels of our study population were similar to those of participants of the Framingham Heart Study and the National Health and Nutrition Examination Survey (20,21). Furthermore,

Table 4 Hazard Ratios for Future CHD According to Non–HDL-C and TG Levels and the TC to HDL-C Ratio in Participants Classified on the Basis of LDL-C Levels

	Non–HDL-C <130 mg/dl	Non–HDL-C ≥130 mg/dl	TG <150 mg/dl	TG ≥150 mg/dl	TC/HDL-C <5	TC/HDL-C ≥5
LDL-C <100 mg/dl	1.00	1.84 (1.12–3.04)	1.00	1.63 (1.02–2.59)	1.00	2.19 (1.22–3.93)
	Non–HDL-C <160 mg/dl	**Non–HDL-C ≥160 mg/dl**				
LDL-C 100–129.9 mg/dl	1.00	1.26 (0.97–1.64)	1.00	1.11 (0.88–1.39)	1.00	1.27 (0.97–1.67)
	Non–HDL-C <190 mg/dl	**Non–HDL-C ≥190 mg/dl**				
LDL-C 130–159.9 mg/dl	1.00	1.38 (1.12–1.69)	1.00	1.30 (1.09–1.54)	1.00	1.46 (1.22–1.74)
	Non–HDL-C <190 mg/dl	**Non–HDL-C ≥190 mg/dl**				
LDL-C ≥160 mg/dl	1.00	1.78 (1.40–2.28)	1.00	1.26 (1.11–1.43)	1.00	1.42 (1.23–1.62)

Hazard ratios were obtained after adjustments for age, sex (total), smoking, waist circumference, physical activity, systolic blood pressure (total), and hormone replacement therapy use (women).
Abbreviations as in Table 1.

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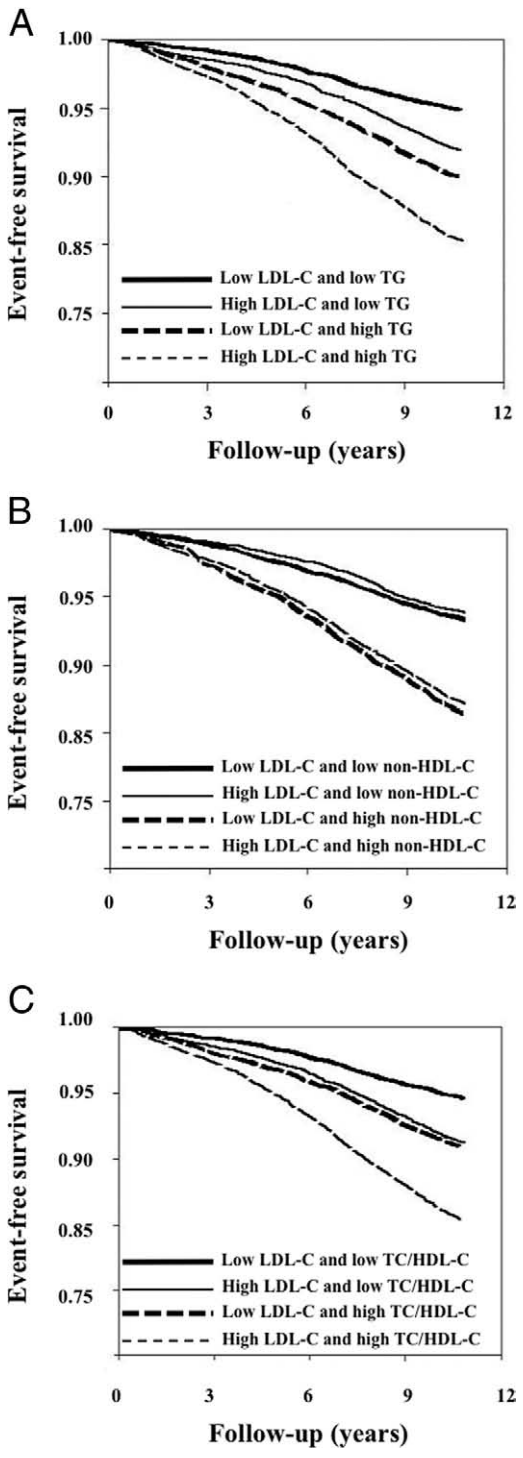

Figure 1 **Kaplan-Meier Survival Curves of Participants Classified Into Subgroups According to Median Lipid Levels**

Kaplan-Meier survival curves of participants classified into subgroups according to median lipid levels: **(A)** low-density lipoprotein cholesterol (LDL-C) (< or ≥150.6 mg/dl) and non–high-density lipoprotein cholesterol (HDL-C) levels (< or ≥177.6 mg/dl), **(B)** LDL-C (< or ≥150.6 mg/dl) and triglyceride (TG) levels (< or ≥128.3 mg/dl), and **(C)** LDL-C levels (< or ≥150.6 mg/dl) and the total cholesterol (TC) to HDL-C ratio (< or ≥4.42).

most of the EPIC-Norfolk participants were at somewhat advanced age at the time of enrollment, a factor that could introduce a survival bias. Also, we have no access to reliable information about the use of lipid-lowering drugs at baseline or during follow-up. This may have led to underestimation of the measures of associations between any lipid variable and CHD risk and therefore, does not negate our findings. Finally, it is important to mention that we did not include stroke as an end point. As a consequence, our results may not be extrapolated to the entire spectrum of cardiovascular disease, as they are limited to CHD. We believe that further studies are required to investigate whether non–HDL-C, TG, or the TC to HDL-C ratio provide additional information to LDL-C with regard to stroke risk.

Conclusions

We observed that irrespective of LDL-C levels, participants with elevated non–HDL-C levels, elevated TG levels, or with an elevated TC to HDL-C ratio have a substantially higher risk of developing CHD. We also found that non–HDL-C levels not only account for the risk associated with LDL-C, but also provide more information about CHD risk associated with elevated lipid levels than LDL-C levels alone. Based on these results, beyond LDL-C levels, CHD risk assessment algorithms as well as lipid targets for lipid-lowering trials may also need to consider other easily available parameters such as non–HDL-C.

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